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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:	
YOSHIKO KUBO, ET AL.	:	EXAMINER: BROWN, COURTNEY A.
SERIAL NO: 10/594,517	:	
FILED: SEPTEMBER 28, 2006	:	GROUP ART UNIT: 1617
FOR: FINE DISPERSION OF SPARINGLY SOLUBLE DRUG AND PROCESS FOR PRODUCING THE SAME	:	

DECLARATION UNDER 37 C.F.R. § 1.132

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

I, Yasuomi Yamasaki, declare that:

1. I am a Japanese citizen, currently residing at 1-71, Toyowaka-cho 2 chome, Toyama-shi, Toyama-ken, Japan.

2. I am a graduate of Kyoto University, and I received a Master's degree in the year 2000 and a Doctor of Philosophy degree in the year 2003 from Graduate School of Kyoto University.

3. I have been employed by Toyama Chemical Co., Ltd. since April 2003 and have been engaged in the research and development of drugs and medicine in our department of Pharmaceutical Research & Technology.

4. I understand the English language, or at least the contents of the Declaration were made clear to me prior to executing the same.

5. I am a named inventor of the above-identified U.S. patent application 10/594,517, filed on September 28, 2006.

6. It is my understanding that claim 1 of the above-identified application is directed to a process for producing a fine dispersion of a poorly soluble drug, wherein the process comprises: suspending the poorly soluble drug in a liquid containing no deflocculant to obtain a suspension; introducing the suspension into a high-pressure homogenizer to subject the suspension to a high-pressure treatment to obtain a dispersion; and adding a deflocculant to the dispersion to deagglomerate aggregated particles contained therein, wherein the poorly soluble drug is 1-cyclopropyl-8-methyl-7-[5-methyl-6-(methylamino)-3-pyridinyl]-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid (hereinafter referred to as "T-3912").

7. I am familiar with the Official Action dated February 24, 2011.

8. I am familiar with the disclosures of Bosch et al. (U.S. Patent 5,510,118) and Yamakawa et al. (Journal of Controlled Release, 86 (2003) 101-103).

9. I respectfully disagree with the Examiner's allegation on page 9, lines 15-22 of the Official Action that the process of Bosch et al. intrinsically produces a fine dispersion of any poorly soluble drug which exhibits superior properties with respect to a narrow particle size distribution and an improved dispersion stability for at least the following reasons.

10. The following experiments were carried out by me or under my direct supervision and control.

11. Materials:

Poorly Soluble Drug: T-3912

Poorly Soluble Drug: Naproxen (as described and exemplified in Bosch et al.)

Deflocculant: 1% aqueous solution of hydroxypropylmethylcellulose (HPMC)

12. Equipment:

High-Pressure Homogenizer: Nanomizer, YSNM-2000AR, manufactured by Yoshida Kikai Co., Ltd.

13. Experimental Procedure:

Example A (Example 1 of the present application)

Poorly Soluble Drug: T-3912

Deflocculant: Added after attrition

3 g of T-3912 was suspended in 47 g of water. The suspension was subjected to high-pressure treatment at 200 MPa 300 cycles using a high-pressure homogenizer (Nanomizer, YSNM-2000AR, manufactured by Yoshida Kikai Co., Ltd.). To 31 g of resultant dispersion, 6 g of 6% aqueous solution of hydroxypropylmethylcellulose (Metholose 60SH-50, manufactured by Shin-Etsu Chemical Co., Ltd.) was added, and the dispersion was subjected to high-pressure treatment at 100 MPa 10 cycles using a high-pressure homogenizer (Nanomizer, YSNM-2000AR, manufactured by Yoshida Kikai Co., Ltd.) to yield 33 g of fine dispersion of T-3912.

Comparative Example B (Comparative Example 1 of the present application)

Poorly Soluble Drug: T-3912

Deflocculant: Present in the premix

3 g of T-3912 was suspended in 47 g of 1% aqueous solution of hydroxypropylmethylcellulose (Metholose 60SH-50, manufactured by Shin-Etsu Chemical Co., Ltd.), and the suspension was subjected to high-pressure treatment at 200 MPa 300 cycles using a high-pressure homogenizer (Nanomizer, YSNM-2000AR, manufactured by Yoshida Kikai Co., Ltd.) to yield 36 g of fine dispersion of T-3912.

Comparative Example C (Example of Bosch et al.)

Poorly Soluble Drug: Naproxen

Deflocculant: Added after attrition

2.5 g of naproxen was suspended in 22.5 g of water. The suspension was subjected to high-pressure treatment at 150 MPa 300 cycles using a high-pressure homogenizer (Nanomizer, YSNM-2000AR, manufactured by Yoshida Kikai Co., Ltd.). To 20 g of resultant dispersion, 4.9 g of 6% aqueous solution of hydroxypropylmethylcellulose (Metholose 60SH-50, manufactured by Shin-Etsu Chemical Co., Ltd.) was added, and the dispersion was subjected to high-pressure treatment at 100 MPa 10 cycles using a high-pressure homogenizer (Nanomizer, YSNM-2000AR, manufactured by Yoshida Kikai Co., Ltd.) to yield 16 g of fine dispersion of naproxen.

Comparative Example D (Example of Bosch et al.)

Poorly Soluble Drug: Naproxen

Deflocculant: Present in the premix

2.5 g of naproxen was suspended in 22.5 g of 1% aqueous solution, of hydroxypropylmethylcellulose (Metholose 60SH-50, manufactured by Shin-Etsu Chemical Co.,

Ltd.), and the suspension was subjected to high-pressure treatment at 150 MPa 300 cycles using a high-pressure homogenizer (Nanomizer, YSNM-2000AR, manufactured by Yoshida Kikai Co., Ltd.) to yield 11 g of fine dispersion of naproxen.

Particle size measurement

The particle size distribution in each of the fine dispersions of each of the above-mentioned examples was measured using a laser diffraction particle size analyzer (LS 13 320, manufactured by Beckman Coulter K.K.). The 50% cumulative diameter and 90% cumulative diameter of each of the above-mentioned examples are shown in Table A below.

14. Experimental Results:

Table A

Examples	Poorly Soluble Drug	Deflocculant	Particle Size Distribution	
			50% Cumulative Diameter (nm)	90% Cumulative Diameter (nm)
Example A	T-3912	Added After Attrition	205	374
Comparative Example B	T-3912	Present in Premix	1443	4810
Comparative Example C	Naproxen	Added After Attrition	514	1061
Comparative Example D	Naproxen	Present in Premix	320	653

15. Discussion:

The inventive fine dispersion of Example A, which was produced by a process comprising suspending *T-3912* in a liquid containing *no deflocculant* to obtain a suspension, introducing the suspension into a high-pressure homogenizer to subject the suspension to a high-pressure treatment to obtain a dispersion, and *subsequently adding a deflocculant* to the dispersion to deagglomerate aggregated particles contained therein, in accordance with an exemplary aspect of the present invention, surprisingly exhibited *superior* properties with respect to a narrow particle size distribution and an improved dispersion stability.

In contrast, the fine dispersion of Comparative Example B, which was produced by a process comprising suspending *T-3912* in a liquid *containing deflocculant* to obtain a suspension, and introducing the suspension into a high-pressure homogenizer to subject the suspension to a high-pressure treatment to obtain a dispersion, exhibited *inferior* properties with respect to an undesirably wide particle size distribution and a reduced dispersion stability.

Meanwhile, the fine dispersion of Comparative Example C, which was produced by a process comprising suspending the poorly soluble drug *Naproxen*, as described in Bosch et al., in a liquid containing *no deflocculant* to obtain a suspension, introducing the suspension into a high-pressure homogenizer to subject the suspension to a high-pressure treatment to obtain a dispersion, and *subsequently adding a deflocculant* to the dispersion to deagglomerate aggregated particles contained therein, exhibited *inferior* properties with respect to an undesirably wide particle size distribution.

In contrast, the fine dispersion of Comparative Example D, which was produced by a process comprising suspending the poorly soluble drug *Naproxen*, as described in Bosch et al., in a liquid *containing deflocculant* to obtain a suspension, and introducing the suspension into a high-pressure homogenizer to subject the suspension to a high-pressure treatment to obtain a dispersion, exhibited *almost identical* properties to Comparative Example C with respect to a particle size distribution.

16. Conclusion:

This evidence clearly demonstrates that a fine dispersion of T-3912, which surprisingly exhibits superior properties with respect to a narrow particle size distribution and an improved dispersion stability, is unexpectedly produced by the process of the present invention comprising suspending T-3912 in a liquid containing no deflocculant to obtain a suspension, introducing the suspension into a high-pressure homogenizer to subject the suspension to a high-pressure treatment

to obtain a dispersion, and adding a deflocculant to the dispersion to deagglomerate aggregated particles contained therein, as presently claimed.

This evidence also demonstrates that contrary to page 9, lines 15-22 of the Official Action, the process of Bosch et al. does not intrinsically produce a fine dispersion of any poorly soluble drug that exhibits superior properties with respect to a narrow particle size distribution and an improved dispersion stability, as alleged by the Office.

In my opinion, Bosch et al. and Yamakawa et al., when considered alone or in combination, fail to recognize that a fine dispersion of T-3912 which exhibits superior properties with respect to a narrow particle size distribution and an improved dispersion stability can be produced by a process comprising suspending T-3912 in a liquid containing no deflocculant to obtain a suspension, introducing the suspension into a high-pressure homogenizer to subject the suspension to a high-pressure treatment to obtain a dispersion, and adding a deflocculant to the dispersion to deagglomerate aggregated particles contained therein, as presently claimed, thereby precluding a *prima facie* case of unpatentability.

In my opinion, Examples similar in composition to Example A above, but comprising, in place of 1% aqueous solution of hydroxypropylmethylcellulose (HPMC), other deflocculants, such as those described in the present specification, would exhibit properties comparable to those of Example A above, with respect to a superior narrow particle size distribution and an improved dispersion stability (See e.g., paragraphs [0022]-[0027], as well as original claims 2 and 3, of Kubo et al. (U.S. 2007/0224282), which is the U.S. pre-grant publication of the originally filed application). I am aware of no reason to believe otherwise.

17. The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so

made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Yasuomi Yamasaki
Signature of Yasuomi Yamasaki

23 May, 2011
Date